

## **REMARKS**

### **I. General Remarks**

Applicants appreciate the Examiner's careful attention to this application. Reconsideration of the application is respectfully requested. Claims 3-5, 19 and 20 are under examination.

### **II. Interview Summary**

A telephonic interview was conducted on November 2, 2010. Present were Examiners S. Swope and R. Mondesi. The parties agreed that the indefiniteness rejection of Claim 19 would be addressed by including a step as to how it is determined whether the compound modulates LKB1 activity. The parties agreed that the indefiniteness rejection of Claim 3 would be addressed by clarifying that the composition is 30% by weight of the LKB1/STRAD/MO25 complex.

### **III. Discussion of Amendments (Support Identified)**

Applicants amend the claims herein. Applicants submit that no new matter has been added to the claims. Applicants make these amendments for the sole purpose of facilitating the expeditious allowance of any subject matter identified as allowable by the Examiner. Applicants make no admission herein that any cancelled or amended claims in their original form is non-patentable; Applicants make no disclaimer of the subject matter of any cancelled or amended claims or dedicate them to the public. If any such disclaimers are believed to have been made, Applicants explicitly rescind them for the purpose of future applications to permit recapture of the original subject matter of any cancelled or amended claims. Applicants reserve the right to file future applications for

letters patent directed to the original subject matter of any cancelled or amended claims. Support for the amendments may be found in the specification as originally filed as discussed below. All references to paragraph numbers refer to the published application.

The specification has been amended to replace the previous sequence listing with a substitute sequence listing. The substitute sequence listing replaces SEQ ID NO: 22 and introduces SEQ ID NO: 159. These sequences do not introduce new matter. The new version of SEQ ID NO: 22 is found in Figure 2 as originally filed, as hMO25 $\beta$ . SEQ ID NO: 159 is found in Figure 2 as originally filed, as cMO25 $\beta$ . The contents of the sequence listing submitted in CRF and the sequence listing submitted on paper are identical.

Claims 3 and 19 have been amended to recite that the AMPK comprises an amino acid sequence having at least 90% homology to residues 1-19 of SEQ ID NO: 110 in a T-loop binding domain and capable of binding LKB1. As illustrated in Fig. 23 and as explained in the legend to Fig. 23 in paragraph [0153] of the published application, the T-loop of AMPK is the major phosphorylation site during LKB1 activation. Paragraph [0327] states that the T-loop domain of AMPK of SEQ ID NO: 110 can serve as the substrate. Note that residues 20-22 of SEQ ID NO: 110 are an artificial poly-arginine tail that was added to enable binding to P81 paper. One of ordinary skill in the art would understand that this artificial poly-arginine tail would not be necessary for LKB1-AMPK interactions. The specification discloses in numerous places that AMPK functions to bind LKB1. The specification supports peptide variants having at least 90% homology to a given sequence in paragraph [0032].

Claims 3 and 19 have been amended to recite that the LKB1 polypeptide comprises at least 90% homology with residues 44-343 of SEQ ID NO: 6. Paragraph [0186] discloses that the catalytic fragment of LKB1 is residues 44-343, and was used for various experiments described in the examples. The figure legend to Figure 7 (paragraph [0137]) states that residues 44-343 comprise the catalytic domain of LKB1. The specification supports peptide variants having at least 90% homology to a given sequence in paragraph [0032].

Claims 3 and 19 have been amended to clarify that STRAD binds to both LKB1 and MO25. The specification teaches in paragraph [0166] that MO25 is associated with LKB1 through STRAD, which binds to both.

Claims 3 and 19 have been amended to recite that the STRAD polypeptide has at least 90% homology to at least one of SEQ ID NO: 9 and SEQ ID NO: 10. Figure 2, as amended on November 28, 2008, shows that SEQ ID NO: 9 is human STRAD  $\alpha$  and SEQ ID NO: 10 is human STRAD  $\beta$ . Human STRAD  $\alpha$  and  $\beta$  are described in paragraph [0026]. The specification supports peptide variants having at least 90% homology to a given sequence in paragraph [0032].

Claims 3 and 19 have been amended to recite that the MO25 polypeptide comprises a sequence having at least 90% homology to with at least one of the listed sequences, including newly inserted SEQ ID NO: 22 and 159. The specification supports peptide variants having at least 90% homology to a given sequence in paragraph [0032]. SEQ ID NO: 22 is found in Figure 2 as originally filed, as hMO25 $\beta$ . SEQ ID NO: 159 is found in Figure 2 as originally filed, as cMO25 $\beta$ . As the Examiner has correctly pointed

out, these were mislabeled in Figure 2A in the amendment of November 28, 2008 as SEQ ID NO: 12 and 14.

Claim 19 has been amended to recite an “*in vitro*” method. Measurement of phosphorylation of a substrate by an LKB1/MO25/STRAD complex is described in the specification at least in paragraphs [0099]-[0106]. Based on the exemplary techniques described (such as protein-protein binding assays and HPLC) one of ordinary skill in the art at the time of filing would have understood that *in vitro* methods were provided in the specification.

Claim 19 has been amended to recite that the substrate polypeptide is of at least 90% homology to the listed sequences. The specification supports peptide variants having at least 90% homology to a given sequence in paragraph [0032].

Claim 19 has been amended to recite in (c) that, if phosphorylation of the substrate compound is significantly increased or decreased, then it will be concluded that the compound modulates LKB1 activity. Applicants submit that it would have been clear to a person of ordinary skill in the art at the time of filing that “modulation” of LKB1 activity means a significant increase or decrease in LKB1 activity.

Claim 16 has been cancelled.

#### **IV. Priority**

On page 8 of the Office Action the Examiner requests that support be identified for SEQ ID NO: 12 and 14 in the earliest priority document. All references in the claims to SEQ ID NO: 12 and 14 have been deleted, and replaced with SEQ ID NO: 22 and 159. Priority document GB0316725.1, filed on July 17, 2003, shows SEQ ID NO: 22 on Figure 2A as hMO25 $\beta$ . GB0316725.1 shows SEQ ID NO: 159 on Figure 2A as cMO25 $\beta$ .

As the claims are fully supported by the earliest priority document, Applicants respectfully submit that the priority date of this application is no later than July 17, 2003.

**V. Sequence Listing Objection**

The Examiner objects to the sequence listing because SEQ ID NO: 16 and 22 were previously the same. Applicants have replaced SEQ ID NO: 22, and it is no longer the same as SEQ ID NO: 16.

**VI. Objections to the Drawings**

A substitute FIG. 2A is submitted correcting the designated SEQ ID NOs.

**VII. Claim Objections**

On page 9 of the Office Action the Examiner objects to Claim 16 as reciting the plural when the singular would be applicable. As Claim 16 is cancelled, this objection is moot.

The Examiner has also provisionally objected to Claims 3-5, 16, 19 and 20 as drawn to non-elected subject matter. As the objection is provisional, it requires no response at the present time.

**VIII. Claim Rejections Under 35 U.S.C. § 112 Paragraph 2**

Claims 3-5, 16, 19 and 20 were rejected as indefinite on pages 9-12 of the Office Action. Each basis for rejection is addressed in turn below.

Claim 19 was rejected as failing to recite a step that accomplished the goal of the method. In response, Claim 19 has been amended to include the step of “(c) concluding that the compound modulates LKB1 activity if the measured phosphorylation of the substrate peptide is significantly increased or decreased in the presence of the

compound.” Applicants respectfully submit that the claim as amended no longer fails to accomplish the goal of the claimed method.

Claim 3 was rejected as indefinite for the stated reason that the phrase “30% by weight of an LKB1 polypeptide, a STRAD polypeptide and a recombinant MO25 polypeptide” is unclear as to whether each polypeptide comprises 30% of the composition by weight or whether the sum of the three polypeptides comprise 30% of the composition by weight. In response, Applicants have amended Claim 3 to recite “30% by weight of a complex of an LKB1 polypeptide, a STRAD polypeptide and a recombinant MO25.” Applicants respectfully submit that this amendment eliminates any indefiniteness.

Claim 3 was rejected for reciting “improper Markush language.” According to MPEP 803.02 “A Markush-type claim recites alternatives in a format such as ‘selected from the group consisting of A, B and C.’ See *Ex parte Markush*, 1925 C.D. 126 (Comm’r Pat. 1925).” The phraseology “wherein R is A, B, C or D” is also proper. MPEP 2173 part I.

Claim 3(a) no longer recites an alternative list of elements. Claim 3(c) as amended recites an alternative list of five sequences, terminated in an “or.” Applicants respectfully submit this is proper Markush language.

Claim 19(a)(i) as amended recites an alternative list of sequences properly terminated with “or.” Claim 19(a)(ii)(A) as amended no longer recites a list of alternative elements. Claim 19(a)(ii)(B) as amended recites a list of alternative elements properly terminated with “or.”

Claims 3 and 19 were rejected as indefinite for the stated reason that the term “conservative substitution” is indefinite. Although Applicants do not admit that this term is indefinite, Claims 3 and 19 have been amended to delete the term “conservative substitution.”

On page 11 Claims 3 and 19 were rejected for the stated reason that the phrase “STRAD polypeptide binds to LKB1 and MO25.” Although Applicants do not admit that this phrase is indefinite, Claims 3 and 19 have been amended to recite “STRAD polypeptide that binds to said LKB1, and binds to MO25.” This language bears out the structure of the LKB1/STRAD/MO25 complex as disclosed in the specification in paragraphs [0134] and [0166].

Claim 3 was rejected for the stated reason that the phrase “a variant of any of the foregoing having at least 65% sequence homology” renders the claim indefinite. As this phrase has been deleted from the claim, applicants submit the rejection is moot.

Finally, Claims 3 and 19 were rejected for the stated reason that the phrase “C-terminal sequence Trp-Glu-Phe” lacks antecedent basis. This term has been amended to be preceded by “a.”

#### **IX. Claim Rejections Under 35 U.S.C. § 112 Paragraph 1 (Enablement)**

On pages 12-16 of the Office Action, Claims 3-5, 16, 19 and 20 were rejected as non-enabled by the specification. The Examiner has taken the position that the specification enables an affinity purified complex comprising a recombinant LKB1 polypeptide comprising residues 44-343 of SEQ ID NO: 6, a recombinant human STRAD protein with a C-terminal Try-Glu-Phe tail, and the recombinant human MO25 of SEQ ID NO: 11; but that the specification does not enable any preparation comprising

an LKB1 with at least 65% homology to positions 44-343 of SEQ ID NO: 6, any STRAD protein, having any structure, with a C-terminal Trp-Glu-Phe tail, and any MO25 protein comprising a sequence with at least 65% sequence homology with any one of SEQ ID NO: 11-15.

Applicants respectfully traverse, and request reconsideration of the rejection.

As noted above, Applicants have amended Claims 3 and 19 in at least the following relevant ways: (1) LKB1 variants are now claimed of at least 90% homology to positions 44-343 of SEQ ID NO: 6; (2) LKB1 polypeptides are now claimed that phosphorylate an AMPK comprising a sequence having at least 90% homology to residues 1-19 of SEQ ID NO: 110 in a T-loop binding domain and capable of binding to LKB1; (3) STRAD polypeptides are now claimed comprising a sequence having at least 90% homology to SEQ ID NO: 9 or 10 (in addition to the C-terminal tail of Trp-Glu-Phe); and (4) MO25 polypeptides are now claimed having at least 90% homology to one of the listed sequences.

Applicants respectfully submit that, based on the specification and the prior art, a person of ordinary skill in the art could prepare the claimed complex comprising an LKB1 of at least 90% homology to positions 44-343 of SEQ ID NO: 6. Although not every such variant would be expected to phosphorylate AMPK as claimed, the high homology requirement would limit the number of variants such that working variants could be identified without undue experimentation.

Applicants respectfully submit that, based on the specification and the art, a person of ordinary skill in the art could prepare the claimed complex comprising an LKB1 able to phosphorylate an AMPK comprising a sequence having at least 90%

homology to residues 1-19 of SEQ ID NO: 110 in a T-loop binding domain and capable of binding to LKB1. The specification teaches that SEQ ID NO: 110 in the T-loop binding domain of AMPK is the target binding region for LKB1, and that Thr-172 is required for phosphorylation in paragraph [0032], and [0327]-[0330]. Based on the high level of required homology, the relatively short sequence, and the established function of the T-loop binding domain, as person of ordinary skill in the art could have practiced the claimed composition without undue experimentation.

Applicants respectfully submit that, based on the specification and the art, a person of ordinary skill in the art could have practiced the claimed composition comprising a complex including the claimed STRAD polypeptide. STRAD variants are now claimed comprising a sequence having at least 90% homology to SEQ ID NO: 9 (human STRAD $\alpha$ ) or 10 (human STRAD $\beta$ ) and a C-terminal tail of Trp-Glu-Phe. Paragraph [0034] of the specification discusses the observation that the complex comprising either STRAD $\alpha$  or STRAD $\beta$  effectively activated AMPK-related kinases. The comparison of STRAD $\alpha$  to STRAD $\beta$  in Figure 10 would provide guidance to one of ordinary skill in the art in determining which regions can be varied and which can be conserved, as it is generally assumed that regions that are conserved between homologous proteins with the same function have a high likelihood of having functional value, whereas regions that are not conserved between homologous proteins with the same function have a lesser likelihood of having functional value. Due to the known function of the claimed C-terminal sequence in binding between MO25 and STRAD to form the LKB1/MO25/STRAD complex, due to the disclosed conserved and variable regions between STRAD $\alpha$  and STRAD $\beta$ , and due to the high level of claimed homology,

a person of ordinary skill in the art could identify working variants of STRAD without undue experimentation (although one would not assume that every such variant would necessarily be a functional variant).

Applicants respectfully submit that, based on the specification and the art, a person of ordinary skill in the art could have practiced the claimed composition comprising a complex including the claimed MO25 polypeptide. MO25 polypeptides are now claimed having at least 90% homology to one of human MO25 $\alpha$ , human MO25 $\beta$ , *Drosophila* MO25, *C. elegans* MO25 $\alpha$ , and *C. elegans* MO25 $\beta$ . One of ordinary skill in the art could look for guidance to Figure 2A, which shows the conserved and variable regions of all five polypeptides, in order to determine which regions of the polypeptides can be varied while still retaining functionality. This guidance, in combination with the high claimed level of homology, would enable one of ordinary skill in the art to determine which variants of the polypeptides could be used successfully without undue experimentation.

For all of the reasons explained above, the Applicants submit that the claims are enabled, and respectfully request withdrawal of the rejections.

**X. Claim Rejections Under 35 U.S.C. § 112 Paragraph 1 (Written Description)**

On pages 16-19 of the Office Action the Examiner rejected Claims 3-5 and 16 as failing to meet the “written description” requirement. The Examiner has taken the position that the specification contains too few specific examples to demonstrate to one of ordinary skill in the art at the time of filing that Applicants “had possession” of the claimed compositions. Applicants respectfully traverse.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was “ready for patenting” such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). See MPEP 2163(a). A specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998).

The written description requirement for a claimed genus may be satisfied through sufficient description of a “representative number” of species by actual reduction to, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see i)(C), above). See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. What constitutes a “representative number” is an inverse function of the skill and knowledge in the art.

In this case, the specification contains an adequate number of examples of the claimed compositions.

In Example 1, which is found in paragraphs [0161]-[0242], Applicants describe the isolation of a LKB1/MO25/STRAD complex from a number of mammalian cell lines by immunoprecipitation. Example 1 describes not just a single version of the LKB1/MO25/STRAD complex as claimed, but the complex comprising both the  $\alpha$  and  $\beta$  isoforms of STRAD and MO25. In an experiment described in paragraphs [0162]-[0164], HeLa cells that had been transfected with a functional LKB1 gene fused to an N-terminal FLAG epitope were used to immunoprecipitate LKB1 from HeLa cell lysate. The transfected HeLa cells were constructed as per Boudeau et al, 2003a (enclosed); Boudeau et al. in turn used constructs as described in Saptoka et al. 2001 (enclosed) (see page 850, column 1, under “DNA Constructs” in Boudeau, which refers to reference 17. Sapkota et al. cloned functional LKB1 from mice (see page 19470, column 2, under “Cloning of Mouse LKB1”). As shown in the attached BLAST search (Exhibit A), positions 44-343 share 96% sequence homology with GenBank accession number NP\_035622.1, which is LKB1 from *Mus musculus*. Therefore this LKB1 falls within the scope of the claims. The transgenic LKB1 co-precipitated with STRAD $\alpha$  and MO25 $\alpha$ .

These would have been the endogenous proteins from the host HeLa cells, so they would have been human STRAD $\alpha$  (SEQ ID NO: 9) and human MO25 $\alpha$  (SEQ ID NO: 11).

In paragraph [0164] an experiment is described in which endogenous LKB1 was precipitated from two lines of cells: human HEK-293 cells and Rat-2 cells (rat embryo fibroblast). As shown in Fig. 3A, in both lines of cells STRAD $\alpha$  and MO25 $\alpha$  co-precipitated with endogenous LKB1. Consequently, the HEK-293 experiment is a working example of a composition comprising endogenous human LKB1 (SEQ ID NO: 6), endogenous human STRAD $\alpha$  (SEQ ID NO: 9), and endogenous human MO25 $\alpha$  (SEQ ID NO: 11).

The Rat-2 experiment is a working example of endogenous rat LKB1 in complex with endogenous rat STRAD $\alpha$  and endogenous rat MO25 $\alpha$ . Enclosed Exhibit B is a BLAST comparison of SEQ ID NO: 9 with STRAD $\alpha$  from other species, including *R. norvegicus* (the last comparison) showing that rat STRAD $\alpha$  is 93% homologous to SEQ ID NO: 9; as a result the STRAD $\alpha$  of the Rat-2 example has at least 90% homology to SEQ ID NO: 9 as claimed. Note that rat STRAD $\alpha$  terminates with Trp-Glu-Phe (WEF). As shown in the HomoloGene pairwise alignment score for MO25 $\alpha$  (Exhibit C), the peptide sequence of rat MO25 $\alpha$  is 99.4% identical to human MO25 $\alpha$  (SEQ NO: 11). As shown in the BLAST comparison of residues 44-343 of SEQ ID NO: 6 to LKB1 from *R. norvegicus* (Exhibit D), rat LKB1 is 96% homologous to residues 44-343 of SEQ ID NO: 6. Therefore it can be said that the Rat-2 experiment is a working example of the composition of Claim 3.

In the first part of paragraph [0166], an experiment is described in which HEK-293 cells were transfected with mouse LKB1 fused to GST and human STRAD $\alpha$  fused to

FLAG. Complexes were then immunoprecipitated comprising transgenic mouse LKB1, transgenic human STRAD $\alpha$ , and endogenous human MO25 $\alpha$  (SEQ ID NO: 11). See Figure 4B, right lane.

In the second part of paragraph [0166] an experiment is described in which complexes were constructed of LKB1/STRAD $\alpha$ /MO25 $\alpha$ , LKB1/STRAD $\alpha$ /MO25 $\beta$ , LKB1/STRAD $\beta$ /MO25 $\alpha$ , and LKB1/STRAD $\beta$ /MO25 $\beta$ . All three peptides were transgenic (mouse LKB1, human STRAD and human MO25). See Figure 4(c), in which the  $\alpha$  isoforms of STRAD and MO25 co-purified with LKB1 in the left lane; in which STRAD $\alpha$  and MO25 $\beta$  co-purified with LKB1 in the next-to-left lane; in which STRAD $\beta$  and MO25 $\alpha$  co-purified with LKB1 in the middle lane; and in which STRAD $\beta$  and MO25 $\beta$  co-purified with LKB1 in the next-to-right lane (the right lane was the negative control). The MO25 $\alpha$  was human MO25 $\alpha$  (SEQ ID NO: 11), the MO25 $\beta$  was human MO25 $\beta$  (SEQ ID NO: 159), the STRAD $\alpha$  was human STRAD $\alpha$  (SEQ ID NO: 9), and the STRAD $\beta$  was human STRAD $\beta$  (SEQ ID NO: 10). Therefore, this experiment provides three additional complexes that are working examples of the claimed composition.

Similar compositions of the LKB1/STRAD/MO25 complex were created in HeLa and HEK-293 cells in the experiments described in paragraphs [0167], [0169]-[0172] (five total separate experiments). These experiments used both the human MO25 $\alpha$  and  $\beta$  isoforms (see paragraph [0170] for an experiment that produced a complex with MO25 $\beta$ ) and the human STRAD $\alpha$  and  $\beta$  isoforms (see paragraph [0171]). Note that the experiment in paragraph [0172] demonstrates that the complex has kinase activity in the presence of either human isoform of both STRAD and MO25.

Thus, Example 1 teaches compositions of all possible combinations of the isoforms of STRAD and MO25 in both human and rat cells in complex with endogenous human LKB1, endogenous rat LKB1, and transgenic mouse LKB1. These are effectively eight working examples of the claimed composition: transgenic mouse LKB1 with human endogenous STRAD $\alpha$  and human endogenous MO25 $\alpha$ , human endogenous LKB1 with human endogenous STRAD $\alpha$  and human endogenous MO25 $\alpha$ , rat endogenous LKB1 with rat endogenous STRAD $\alpha$  and rat endogenous MO25 $\alpha$  (from Rat-2 cells); mouse transgenic LKB1 with human transgenic STRAD $\alpha$  and human endogenous MO25 $\alpha$ , mouse transgenic LKB1 with human transgenic STRAD $\alpha$  and human transgenic MO25 $\alpha$ , mouse transgenic LKB1 with human transgenic STRAD $\beta$  and human transgenic MO25 $\alpha$ , mouse transgenic LKB1 with human transgenic STRAD $\alpha$  and human transgenic MO25 $\beta$ ; mouse transgenic LKB1 with human transgenic STRAD  $\beta$  and human transgenic MO25  $\beta$ .

Example 2, presented in paragraphs [0243]-[0326], describes further experiments involving the claimed compositions.

The experiment described in paragraphs [0246]-[0247] purified two LKB1/STRAD/MO25 complexes from rat liver extract. For both complexes (AMPKK1 and AMPKK2) endogenous rat LKB1 was co-precipitated with endogenous rat STRAD $\alpha$  and MO25 $\alpha$ . As explained above, rat LKB1, STRAD $\alpha$  and MO25 $\alpha$  are all at least 90% homologous to the claimed SEQ ID NOs, and such complexes are thus working examples of the claimed composition.

The experiments described in paragraphs [0250] and [0334] describe the construction of LKB1/STRAD/MO25 complexes in HEK-293T cells in which transgenic

LKB1, STRAD, and MO25 were used. Complexes containing all possible combinations of STRAD and MO25 isoforms were tested for kinase activity. As shown in Fig. 15, all four complexes of wild-type LKB1 (STRAD $\alpha$ /MO25 $\alpha$ , STRAD $\alpha$ /MO25 $\beta$ , STRAD $\beta$ /MO25 $\alpha$ , and STRAD $\beta$ /MO25 $\beta$ ) showed significant kinase activity (see lanes 6-9). Figure 22 shows that twelve different AMPK-like proteins were activated by all four complexes. These experiments provide four additional working examples of the claimed compositions.

The experiment described in paragraph [0253] describes the immunoprecipitation of transgenic LKB1 with endogenous MO25 $\alpha$  and endogenous STRAD $\alpha$  from HeLa cells. The HeLa cells normally do not express LKB1, and so active LKB1 was introduced. When HeLa cells were transformed with LKB1, AMPK kinase activity was detected, whereas in untransformed cells there was none. This is another working example of the claimed composition in human cells, in which LKB1 is transgenic (mouse) and MO25 $\alpha$  and STRAD $\alpha$  are endogenous (human).

Example 2 provides two working examples of endogenous rat LKB1, MO25 $\alpha$  and STRAD $\alpha$  from rat liver extract; additional working examples of transgenic mouse LKB1 with transgenic versions of all possible variations of both isoforms of human STRAD and MO25; and additional working examples of complexes of transgenic mouse LKB1 with endogenous human MO25 $\alpha$  and endogenous human STRAD $\alpha$ .

Applicants respectfully submit that these examples, in several cell lines of two species, including polypeptides from three species that are both endogenous and transgenic, would have indicated to one of ordinary skill in the art at the time of filing that applicants has in their possession the claimed compositions of Claims 3-5.

## **XI. Claim Rejections Under 35 U.S.C. § 102**

Claims 3-5, 16, 19 and 20 have been as anticipated over various references. These references include Tang (2000), Den Daas (2000), Boudeau (2003), and Hardie (2005). As discussed above, Applicants submit that the priority date of this application is no later than July 17, 2003. Hardie was published in 2005, and Boudeau was published in October of 2003. As these references were published after July 17, 2003, they are not prior art. Applicants traverse the rejections based on Hardie and Boudeau on this basis, and no further discussion of these references is included in this response.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicants respectfully submit that neither Tang nor Den Daas teach every element of the rejected claims, inherently or explicitly.

Tang teaches a composition comprising a protein having 81% sequence identity with SEQ ID NO: 11. Without analyzing this reference further, Applicants point out that Claims 3 and 19, as amended, are directed to a LKB1/STRAD/MO25 complex of at least 90% sequence identity with SEQ ID NO: 11. Therefore Tang does not teach this element of the claims, and Tang does not anticipate the claims.

Den Daas teaches a polypeptide of SEQ ID NO: 2, which the Examiner has computed to have 100% sequence homology with SEQ ID NO: 11 (human MO25 $\alpha$ ). The Examiner cites Den Daas on page 12, lines 21-26 to teach the production of transgenic human MO25 $\alpha$ . The Examiner cites page 17 of Den Daas to teach producing antibodies that recognize the transgenic polypeptides, and using the same to purify the polypeptides

by affinity chromatography. The Examiner then concludes that the remaining claim elements are inherent in the disclosure of Den Daas.

Applicants respectfully traverse and request reconsideration of the rejection.

At the very least, it was not inherent that using affinity chromatography with antibodies against transgenic human MO25 $\alpha$  would produce a composition comprising the LKB1/STRAD/MO25 complex as claimed.

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) An invitation to investigate is not an inherent disclosure where a prior art reference discloses no more than a broad genus of potential applications of its discoveries. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004).

The teaching in Den Daas that a polypeptide may be purified by affinity chromatography using an antibody is not limited as to the type of cell. As explained in the specification in paragraph [0161], some types of cancer cell do not express functional LKB1. For example, HeLa cells and G361 melanoma cells do not express LKB1 (see the specification at paragraphs [0009], [0162], [0244], and [0253]). Indeed, in the

experiments described in the examples, HeLa cells were used as LKB1 knockouts because of this property. However, HeLa and C361 melanoma do express MO25 (see the specification in paragraph [0113]). As a result, if samples from these commonly used cell lines were purified by affinity chromatography with an antibody that recognizes MO25, the product would not be in complex with LKB1 as claimed, because these cells do not express LKB1. As a result, depending on which type of cell was the subject of the purification, there is no more than a mere "possibility or probability" that the result would be a complex as claimed.

Page 12 states that the polypeptides disclosed in the specification may be produced by genetically engineering a host; hosts are listed including bacterial cells, yeast cells, and HeLa cells. Those types of cells do not express LKB1, so the transgenic product would not be in complex as claimed. The production of antibodies against uncomplexed human MO25 $\alpha$  (which would be the product of expressing human MO25 $\alpha$  in bacteria, yeast, and HeLa cells) will not always produce an antibody that is able to recognize MO25 in complex with STRAD and LKB1. It is known in the art that antibody recognition sites may be occluded if the target polypeptide is in contact with other polypeptides, as occurs when a polypeptides complex to form a larger protein. Therefore it cannot be assumed that an antibody that is developed to recognize an uncomplexed polypeptide (such as human MO25 $\alpha$ ) will function to recognize the complexed polypeptide.

Furthermore, Den Daas provides no guidance as to what types of samples or sources can be subject to purification. It is possible that a given sample will contain uncomplexed MO25 $\alpha$ , or MO25 $\alpha$  incorporated in a complex other than

LKB1/STRAD/MO25. As explained in paragraph [0178] of the published application, MO25 recognizes a C-terminal motif that is found not only in STRAD, but in at least 20 other known human proteins. This leaves open the possibility that MO25 forms complexes with other proteins. As a result, the purification of human MO25 $\alpha$  could produce a composition comprising a significant quantity of complexed products other than LKB1/STRAD/MO25, and could also contain a significant quantity of uncomplexed MO25.

Finally, Den Daas provides only a broad and prophetic description of the expression of the polypeptide in any cell, and purifying the polypeptide from no specified source. Applicants respectfully submit that this is what is meant in MPEP 2112 IV by “An invitation to investigate is not an inherent disclosure where a prior art reference discloses no more than a broad genus of potential applications of its discoveries” (citing *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004)).

In summary, Den Daas clearly does not explicitly teach every element of the claims. Applicants respectfully submit that Den Daas does not inherently teach the elements of the MO25 polypeptide in complex with STRAD and LKB1 as claimed. Accordingly, Applicants respectfully request withdrawal of the rejection.

## **XII. Claim Rejections Under 35 U.S.C. § 103**

On pages 21-23, Claims 19 and 20 are rejected as obvious over the combination of Boudeau and Mohamed in view of Hong (2003). As explained above, Boudeau is not prior art relative to this application. The Hong article is dated July 22, 2003, which is

after July 17, 2003. Therefore Hong is not prior art relative to this application, either.

Accordingly, Applicants respectfully request withdrawal of the rejection.

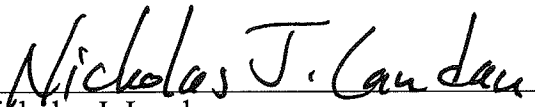
## CONCLUSION

Applicants respectfully request the consideration of the enclosed remarks and entry of the following submission into the record, in response to the Office Action. Reconsideration in light of this submission is respectfully requested. If additional action is required that may benefit from a telephone call, Applicants invite a call to its attorney of record, Nicholas J. Landau (Reg. No. 57,120). E-mail correspondence and transactions to [nlandau@babco.com](mailto:nlandau@babco.com) are authorized and encouraged.

Applicants have diligently sought to comply with all requirements and to correct all informalities and rejections. The Application is believed to be in condition for allowance, and a timely Notice of Allowance is respectfully requested.

Respectfully submitted,  
BRADLEY ARANT BOULT CUMMINGS LLP

14 Dec. 2010  
Date

  
Nicholas J. Landau  
Reg. No. 57,120